0;



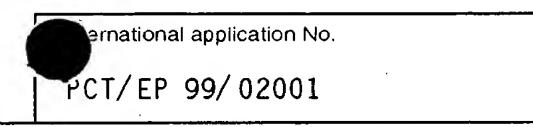
INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER see Notification	of Transmittal of International Search Report
0098125-VEmi		/220) as well as, where applicable, item 5 below.
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/EP 99/02001	24/03/1999	29/03/1998
Applicant	2 17 0 37 1 7 7 7	27/03/17/0
Уррпоції		
MERCK PATENT GMBH et al.		
TIEROR TATERT GIBTI CC at.		
This International Search Report has been according to Article 18. A copy is being tra	n prepared by this International Searching Au ansmitted to the International Bureau.	uthority and is transmitted to the applicant
This International Search Report consists It is also accompanied by	of a total of sheets. a copy of each prior art document cited in the	is report.
Basis of the report		
	international search was carried out on the baless otherwise indicated under this item.	asis of the international application in the
the international search w Authority (Rule 23.1(b)).	as carried out on the basis of a translation of	f the international application furnished to this
• • • • • • • • • • • • • • • • • • • •	•	international application, the international search
	onal application in written form.	
filed together with the inte	ernational application in computer readable fo	orm.
furnished subsequently to	this Authority in written form.	
furnished subsequently to	this Authority in computer readble form.	
	osequently furnished written sequence listing is filed has been furnished.	does not go beyond the disclosure in the
the statement that the info furnished	ormation recorded in computer readable form	is identical to the written sequence listing has been
2. X Certain claims were fou	nd unsearchable (See Box I).	
3. Unity of invention is lac	king (see Box II).	
4. With regard to the titie ,		
the text is approved as su	bmitted by the applicant.	
The text has been establis	shed by this Authority to read as follows:	
USE OF ROR RECEPTORS I ATHEROSCLEROSIS	FOR SCREENING SUBSTANCES US	SEFUL FOR THE TREATMENT OF
,		
5. With regard to the abstract,		
	•	ority as it appears in Box III. The applicant may, eport, submit comments to this Authority.
6. The figure of the drawings to be publ	ished with the abstract is Figure No.	
as suggested by the appl	cant.	X None of the figures.
because the applicant fail	ed to suggest a figure.	-
because this figure better	characterizes the invention.	

Form PCT/ISA/210 (first sheet) (July 1998)





Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. X	Claims Nos.: 14-16 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: see FURTHER INFORMATION sheet PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	ernational Searching Authority found multiple inventions in this international application, as follows:
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark	k on Protest The additional search fees were accompanied by the applicant's protest.
	No protest accompanied the payment of additional search fees.
	·

International Application No. PCT/ EP 99 / 02001

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The description as well as claims 14-16 doe not comply with the prescribed requirements to the extent that a meaningful search for these claims is not possible. The description does not sufficiently disclose the inventions of claim 14-16 (i.e. the substances selected by the screening method) by technical features of the substances themselves so as to allow the formulation of a meningful search. In consequence the search for the second medical indication cannot be effected.

International Application No. PCT/EP 99 \(\Delta 2001 \)

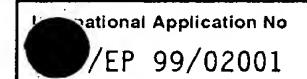
FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 14-16

The description as well as claims 14-16 doe not comply with the prescribed requirements to the extent that a meaningful search for these claims is not possible. The description does not sufficiently disclose the inventions of claim 14-16 (i.e. the substances selected by the screening method) by technical features of the substances themselves so as to allow the formulation of a meningful search. In consequence the search for the second medical indication cannot be effected.

INTERNATIONAL SEARCH REPORT





A. CLASSIFICATION OF SUBJECT MATTER IPC 6 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 6 GO1N CO7K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

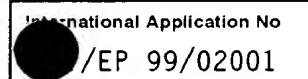
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 721 096 A (KARATHANASIS SOTIRIOS K ET AL) 24 February 1998 see the whole document	1-11,13, 17
X	LAVRENTIADOU, SOPHIA (1) ET AL: "Modulation of the ApoCIII promoter activity by heterodimers of ligand dependent nuclear receptors RXR -alpha-RAR -alpha, RXR -alpha-T3R-beta and RXR -alpha-PPAR-alpha." CIRCULATION, (1995) VOL. 92, NO. 8 SUPPL., PP. I291. MEETING INFO.: 68TH SCIENTIFIC SESSION OF THE AMERICAN HEART ASSOCIATION ANAHEIM, CALIFORNIA, USA NOVEMBER 13-16, 1995 ISSN: 0009-7322., XP002088668 *Abrégé: dernière ligne*	1-13,17

Further documents are listed in the continuation of box C.	χ Patent family members are listed in annex.		
 Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report		
14 June 1999	21/06/1999		
Name and mailing address of the ISA	Authorized officer		
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoekstra, S		

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INTERNATIONAL SEARCH REPORT





0.40	W A DOCUMENTO CONCIDENTE TO DE DEL EVANT	/EP 99/02001
	Citation of decrement with indication where consists, of the relevant passages	Relevant to claim No.
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Helevani to claim No.
T	VU-DAC, NGOC ET AL: "Retinoids increase human Apo C-III expression at the transcriptional level via the retinoid X receptor: contribution to the hypertriglyceridemic action of retinoids" J. CLIN. INVEST. (1998), 102(3), 625-632 CODEN: JCINAO;ISSN: 0021-9738, XP002088669	1-13,17
A	JANUZZI, JAMES L. ET AL: "Characterization of the mouse apolipoprotein Apoa-1/Apoc-3 gene locus: Genomic, mRNA, and protein sequences with comparisons to other species" GENOMICS (1992), 14(4), 1081-8 CODEN: GNMCEP; ISSN: 0888-7543, XP002088670 see the whole document	1-13,17
A	OGAMI, K. ET AL.: "Promoter elements and factors required for hepatic and intestinal trasncription of hte human apoCIII gene" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 17, 1990, pages 9808-9815, XP002088671 cited in the application see figure 3	1-13,17
Α	TAYLOR, D.G. ET AL.: "Characterisation of a dominant negative mutant form of the NHF-4 orphan receptor." NUCLEIC ACIDS RESEARCH, vol. 24, no. 15, 1996, pages 2930-2935, XP002088672 see the whole document	1-13,17
Α .	JUMP D B ET AL: "Dietary fat, genes, and human health." ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1997) 422 167-76. REF: 70 JOURNAL CODE: 2LU. ISSN: 0065-2598., XP002088673 United States see the whole document	1-13,17

INTERNATIONAL SEARCH REPORT

In ion on patent family members

EP 99/02001

		itent document I in search report		Publication date	Patent family member(s)		Publication date	
<u> </u>	US	5721096 A		24-02-1998	NONE			_
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

International application No.			FOR FURTHER ACT		fication of Transmittal of International ary Examination Report (Form PCT/IPEA/416)	
			International filing date (day	//month/year)	Priority date (day/month/year)	
			24/03/1999		29/03/1998	
Internationa G01N33/	_	nt Classification (IPC) or	national classification and IPC			
Applicant		TAT ONDUITATI				
MERCK	AIL	ENT GMBH et al.				
		•	mination report has been pr t according to Article 36.	epared by this li	nternational Preliminary Examining Authority	
2. This F	REPO	RT consists of a total	of 6 sheets, including this o	over sheet.		
b (s	een a see R	mended and are the b	asis for this report and/or sl 607 of the Administrative Ir	neets containing	tion, claims and/or drawings which have rectifications made before this Authority the PCT).	
3. This r	eport ⊠	contains indications re Basis of the report	elating to the following items	; :		
11		Priority				
Ш	\boxtimes	Non-establishment o	f opinion with regard to nove	elty, inventive st	ep and industrial applicability	
V					nventive step or industrial applicability;	
VI		Certain documents	•	ion.		
VII			e international application			
VIII	×	Certain observations	on the international applica	tion		
Date of sub	omissi	on of the demand		Date of completion	of this report	
05/10/1999				23.06.2000		
	exam	g address of the internation in ining authority: opean Patent Office	onal	Authorized officer	S. S	
D-80298 Munich			•	Stricker, J-E		
Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465			·	Talanhona No. +49	2 80 2300 8305	



International application No. PCT/EP99/02001

I. Basis of the report

1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

	1110	report since they d	o not comain amonaments.				
	Description, pages:						
	1-46	6,52-54	as originally filed				
	Clai	ims, No.:					
	1-17	7	as originally filed				
	Dra	wings, sheets:					
	1/17	7-17/17	as originally filed				
•	TL -						
2.	ine	amenaments nav	e resulted in the cancellation of:				
		the description,	pages:				
		the claims,	Nos.:				
		the drawings,	sheets:				
3.		•	een established as if (some of) the amendments had not been made, since they have been beyond the disclosure as filed (Rule 70.2(c)):				
4.	Add	ditional observation	ns, if necessary:				
111.	Noi	n-establishment c	of opinion with regard to novelty, inventive step and industrial applicability				
	•		ne claimed invention appears to be novel, to involve an inventive step (to be non-obvious), cable have not been examined in respect of:				
		the entire interna	tional application.				
	×	claims Nos. 14, 1	5, 16.				
be	cau	se:					



International application No. PCT/EP99/02001

×	the said international application, or the said claims Nos. 15 and 16, as regards industrial applicability, relate to the following subject matter which does not require an international preliminary examination (<i>specify</i>):
	see separate sheet
	the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
	the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
×	no international search report has been established for the said claims Nos. 14.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-13, 15-17

No: Claims -

Inventive step (IS) Yes: Claims -

No: Claims 1-13, 15-17

Industrial applicability (IA) Yes: Claims 1-13, 15, 16

No: Claims -

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet



Section III

Claims 15 and 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 (i) and (v) PCT. Consequently, no preliminary examination will be done with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

The first document cited as [X] in the ISR discloses the regulation of apoA-I by ARP-I and RXR α which are different from ROR. The second document cited as [X] in the ISR teaches that the apoC-III promoter contains a HRE which is recognized by HNF-4, the latter being an orphan nuclear receptor but different from ROR. These documents are therefore not considered to be of particular relevance.

The following documents (D) have been <u>cited by the applicant</u> in the description; the numbering will be adhered to in the rest of the procedure:

- D1: WO-A-95 27202 (cited on p.2, l.12)
- D2: VU-DAC, NGOC et Al: "Transcriptional Regulation of Apolipoprotein A-I Gene Expression by the Nuclear Receptor RORα", J. Biological Chemistry (1997), 272(36), p.22401-22404 (cited as Ref.53 on p.2, I.29).
- 1. Document D1, which is considered to represent the most relevant state of the art, discloses (cf. abstract and the claims) a screening method from which the subject-matter of claims 1, 3 and 16 differs in that the selected substances have antiatherosclerotic properties / are useful in the treatment of lipid metabolism dysfunctions.

The subject-matter of claims 1, 3 and 16 is therefore novel (Art. 33(2) PCT).

The problem to be solved by the present invention may therefore be regarded as to identify other metabolic pathways that are regulated by a ROR, that is, other genes whose expression can be modulated by a ROR, i.e. genes whose promoter

EXAMINATION REPORT - SEPARATE SHEET

contains a ROR responsive element (RORE).

The solution proposed in claims 1, 3 and 16 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

D2 discloses (cf. abstract) that RORα1 is an activator of apoA-I gene which contains a RORE (in the rat and mouse promoter). Since HDL and its major apolipoprotein apoA-I confer protection against atherosclerosis, the skilled person would have been sufficiently motivated to use the screening method of D1 in order to first identify substances having antiatherosclerotic properties / which are useful in the treatment of lipid metabolism dysfunctions, and second prepare a pharmaceutical composition useful for the treatment and/or prevention of atherosclerosis in humans or animals. Thus, the subject-matter of claims 1, 3 and 16 does not involve an inventive step (Art. 33(3) PCT).

- Dependent claims 2 and 4-13 do not contain any features which, in combination 2. with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, the reasons being as follows:
 - Claims 4-11 relate to vector constructions and to the use of compounds a) which are common in the art (cf. e.g. D1). ROR α (claims 2 and 13) is disclosed in D1 and D2.
 - Having selected a substance by the screening method of claim 3 (cf. item 1 b) above), the skilled person would have been sufficiently motivated to determine the effect of the said substance on the expression of apo C-III because it was known that apo C-III (cf. item 3 below) and apoA-I have adverse effects. Thus, the subject-matter of claim 12 does not involve an inventive step (Art. 33(3) PCT).

Only a screening method wherein the effect on the expression of apo C-III is determined by using ROR receptors and/or their response element would appear to meet the requirements of Art. 33(3) PCT because it was not known that RORs are involved in the regulation of the expression of the apoC-III gene.

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

- The subject-matter of claim 15 is not disclosed in the known prior art and 3. therefore would appear to be novel (Art. 33(2) PCT). Nevertheless, as disclosed in the present application (cf. p.3, l.15 to p.4, l.39), the role of apoC- III in hypertriglyceridemia, which leads to atherosclerosis, is well known in the art. Thus, the skilled person would regard it a normal design procedure to combine all the features set out in claim 15. The subject-matter of the said claim does therefore not involve an inventive step (Art. 33(3) PCT).
- Since the method of claims 3-13 is novel, the subject-matter of claim 17 can be 4. considered as being novel as well (Art. 33(2) PCT. However, the said subjectmatter would not appear to meet the requirements of Art. 33(3) PCT for the same reasons as those set out in item 2.b) above.

Section VIII

- Claims 6 and 7 are not clear (Art. 6 PCT) for the following reasons: 1.
 - "the toxic prodrug" in claim 6 lacks an antecedent **a**)
 - b) an inconsistency exists between the description and claim 6 as regards the gene whose expression is controlled ("suicide gene for selection" on p.10, l.1 and "selectable gene" in step a) of claim 6).
 - step b) in claim 7 and the description on p.10, l.26 should apparently read C) "another plasmid is created..."
- 2. Substances selected by a method of screening according to the present application (cf. p.11, l.39) do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT). One should bear in mind that no search was established for such selected substances.